TRANSPARENCY COMMITTEE

OPINION

4 November 2009

RANEXA 375 mg extended release tablet
Pack of 60 (CIP: 394 370-7)

RANEXA 500 mg extended release tablet
Pack of 60 (CIP: 394 373-6)

RANEXA 750 mg extended release tablet
Pack of 60 (CIP: 394 375-9)

Applicant: A. MENARINI FARMACEUTICA INTERNAZIONALE Srl

Ranolazine

ATC Code: C01EB18

List I

Date of marketing authorisation (centralised): July 9, 2008

Reason for request: Inclusion on the list of medicines reimbursed by National Health Insurance and approved for use by hospitals.
1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Ranolazine

1.2. Background
Ranolazine is a late sodium current inhibitor whose mechanism of action is uncertain.

1.3. Indication
“Ranexa is indicated in combination with symptomatic treatment of patients suffering from stable angina (chest pains) poorly controlled or intolerant to first-line antianginals (such as betablockers and/or calcium channel blockers).”

1.4. Dosage
“Patients taking Ranexa must be given the product leaflet and a ‘Patient Alert Card’; these documents, accompanied by the list of all their treatments, must be presented at each medical consultation. Ranexa is available in the form of 375 mg, 500 mg and 750 mg extended release tablets.

Adults: the initial recommended dosage of Ranexa is 375 mg twice daily. After 2 to 4 weeks, increase the dose to 500 mg twice daily and, according to the patient’s response, consider another increase to the maximum recommended dose of 750 mg twice daily (see SPC). In the event of treatment-related side effects (e.g. dizziness, nausea or vomiting), it may be useful to decrease the dose gradually from 500 mg to 375 mg twice daily. Should symptoms persist despite decreasing the dose, discontinue treatment.

Concomitant treatment with CYP3A4 and P-glycoprotein (P-gp) inhibitors: caution is advised when increasing the dose for patients treated with moderate CYP3A4 inhibitors (e.g. diltiazem, fluconazole, erythromycin) or P-gp inhibitors (e.g. verapamil, ciclosporin). Concomitant administration of powerful CYP3A4 inhibitors is contraindicated (see SPC).

Renal impairment: caution is advised when increasing the dose for patients with mild to moderate renal impairment (creatinine clearance 30–80 ml/min). Ranexa is contraindicated for patients with severe renal impairment (creatinine clearance <30 ml/min) (see SPC).

Hepatic impairment: caution is advised when increasing the dose for patients with mild hepatic impairment. Ranexa is contraindicated for patients with moderate to severe hepatic impairment (see SPC).

Elderly patients: special care is required when increasing the dose for elderly patients. An increase in exposure to ranolazine is possible for elderly patients due to the age-related decrease in renal function. The incidence of adverse effects was higher among the elderly (see SPC).

Low body weight: the incidence of adverse effects was higher among patients with a low body weight (≤ 60 kg). Special care is required when increasing the dose for patients with a low body weight (see SPC).

Congestive heart failure: special care is required when increasing the dose for patients with moderate to severe congestive heart failure (NYHA III–IV) (see SPC).

Paediatric population: Ranexa is not recommended for children below the age of 18 due to a lack of data on safety and efficacy. Ranexa tablets should be swallowed whole, without being chewed, crushed, or chopped. To be taken during or between meals.”
2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2008)
C : Cardiovascular system
C01 : Medicinal products in cardiology
C01E : Other cardiology medicinal products
C01EB : Other cardiology medicinal products
C01EB 18 : Ranolazine

2.2. Medicines in the same therapeutic category
Ranolazine is the first medicinal product in this therapeutic class.

2.3. Medicines with a similar therapeutic aim:
All products indicated for patients with stable angina (chest pains) poorly controlled or intolerant to beta-blockers and/or calcium channel blockers:
- Long-acting nitrates: Isosorbide, trinitrine
- Nicorandil: ADANCOR, IKOREL, indicated for “prophylactic treatment of exertional angina alone or combined with other antianginals”
- Ivabradine: PROCORALAN, indicated for “symptomatic treatment of chronic stable angina in patients with normal sinus rhythm, who have a contraindication or intolerance to betablockers (in the event of intolerance or contraindication to betablockers)”

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy
The efficacy and safety of RANEXA have been evaluated in 5 randomised double-blind studies:
- two single therapy studies:
  - the MARISA study (CVT 3031), which aims to compare the efficacy of three doses of RANEXA (500 mg twice daily, 1,000 mg twice daily and 1,500 mg twice daily) to that of the placebo in terms of total exercise duration (n=191).
  - the RAN 080 study, the aim of which was to compare the efficacy of RANEXA with atenolol 100 mg/day in terms of time until occurrence of chest pains (n=158); this phase II study was conducted with RANEXA 400 mg immediate-release, a different pharmaceutical form to the one marketed. This opinion will therefore not dwell upon this study.
- three combined therapy studies:
  - the CARISA study (CVT 3033), which aims to compare the efficacy of RANEXA (750 mg twice daily and 1,000 mg twice daily) combined with amlodipine 5 mg/day, atenolol 50 mg/day or diltiazem 180 mg/day with that of the placebo in terms of total exercise duration (n=823).
  - the ERICA study (CVT 3037), which aims to compare the efficacy of RANEXA 1000 mg twice daily with that of the placebo in terms of the number of angina attacks per week (n=565). As the dose studied here was greater than the maximum dose authorised in the MA (750 mg twice daily), this opinion will not dwell upon this study.
  - the MERLIN study (3036), which aims to compare the efficacy of RANEXA 1000 mg twice daily with that of the placebo in terms of reduced cardiovascular events (cardiovascular deaths, myocardial infarction and recurring ischaemic events) in 6,560 patients with acute coronary syndrome monitored over 12 months. As this study is the only morbidity-mortality study available, it will be detailed in this opinion although the dosage studied was higher than the maximum dose authorised in the MA.
The company has also submitted a combined analysis of the CARISA and ERICA\(^1\) studies regarding the efficacy of RANEXA according to the patients’ age. As for the population of diabetic patients, the company submitted two post hoc analyses of the CARISA\(^2\) and MERLIN\(^3\) studies.

The patient subgroups according to age and diabetic patients studied in these analyses were created \textit{a posteriori} giving the results an exploratory value only. Given the methodological limits of these analyses, their results will not be taken into account.

### 3.1.1. Single therapy studies: MARISA study (CVT 3031)

\textbf{Method:} a randomised, double-blind, cross-over, dose-finding study comparing RANEXA 500 mg twice daily, 1000 mg twice daily and 1500 mg twice daily to placebo on 191 patients with stable angina monitored over 4 weeks.

\textbf{Inclusion criteria}: patients aged over 21 with:
- exertional angina (relieved by rest and/or administration of trinitrine) stabilised for at least 3 months with betablocker treatment or a calcium channel blocker or long-acting nitrates,
- history of coronary disease defined as at least one of the following events: stenosis of \( \geq 60\% \) of a major coronary artery, myocardial infarction, cardiac ischaemia.

\textbf{Treatments}:
- Treatment A: RANEXA 500 mg twice daily
- Treatment B: RANEXA 1000 mg twice daily
- Treatment C: RANEXA 1500 mg twice daily
- Treatment D: Placebo

The 191 patients were included in the 4 following treatment sequences: ABCD (n=47), BDAC (n=49), CADB (n=50) and DCBA (n=45).

\textit{NB: Only the results regarding the MA-approved dosage (RANEXA 500 mg twice daily) will be presented.}

\textbf{Primary endpoint}: difference in total exercise duration (TED) assessed using a treadmill exercise capacity test (conducted 12 hours after taking the treatment).

\textbf{RESULTS:}
After 4 weeks of treatment, the total exercise duration (TED) was significantly improved with RANEXA 500 mg twice daily compared to placebo: difference = 23.8 seconds [8.2; 39.4], \( p=0.003 \).

### 3.1.2. Combined therapy studies

- **CARISA study (CVT 3033)**

\textbf{Method:} randomised, double-blind study comparing RANEXA 750 mg twice daily and 1000 mg twice daily combined with ongoing antianginal treatments to placebo on 791 patients with stable angina not sufficiently controlled with diltiazem 180 mg/day, atenolol 50 mg/day* or amlodipine 5 mg/day monitored over 12 weeks.

*The average MA-approved dosage of atenolol in the indication “Prophylaxis of angina attacks” is \textit{one 100 mg tablet per day; this may be increased to 2 tablets per day if necessary}.

\begin{thebibliography}{9}
\bibitem{2} Timmis et al “Effects of ranolazine on exercise tolerance and HbA1c in patients with chronic angina and diabetes” Eur Heart J;27:42-8
\end{thebibliography}
Inclusion criteria: patients aged over 21 with:
- exertional angina (that can be relieved by rest and/or the administration of trinitrine) stabilised for at least 3 months,
- history of coronary disease defined as at least one of the following events: stenosis of \(\geq 60\%\) of a major coronary artery, myocardial infarction, coronary disease.

Treatments:
- RANEXA 750 mg twice daily, n=272
- RANEXA 1000 mg twice daily, n=261
- Placebo, n=258

*NB: Only the results regarding the MA-approved dosage (RANEXA 750 mg twice daily) will be presented.*

Primary endpoint: difference in total exercise duration (TED) after 12 hours of treatment, assessed using a treadmill exercise capacity test conducted 12 hours after taking the treatment.

**RESULTS:** on an intention-to-treat basis (see table 1)
Baseline patient characteristics were similar. On inclusion, the TED was around 7 minutes (416.5 seconds).

Concomitant treatments were:
- diltiazem 180 mg/day: 26% of patients,
- atenolol 50 mg/day: 43% of patients. The mean MA-approved dosage of atenolol in the indication "Prophylaxis of angina attacks" is "one 100 mg tablet per day; this may be increased to 2 tablets per day if necessary".
- amlodipine 5 mg/day: 31% of patients.

Table 1: change in TED after 12 weeks of treatment (in seconds)

<table>
<thead>
<tr>
<th></th>
<th>RANEXA 750 mg twice daily n=272</th>
<th>RANEXA 1000 mg twice daily n=261</th>
<th>Placebo n=258</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference compared to baseline</td>
<td>+ 115.4 [-276; 516]</td>
<td>+ 115.8 [-253; 448]</td>
<td>+ 91.7 [-240; 527]</td>
</tr>
<tr>
<td>Difference compared to placebo [95% CI]</td>
<td>23.7 [2.3; 45.1]</td>
<td>24 [2.4; 45.7]</td>
<td></td>
</tr>
<tr>
<td>p compared to placebo</td>
<td>0.03</td>
<td>0.029</td>
<td></td>
</tr>
</tbody>
</table>

After 12 weeks of treatment, in patients inadequately controlled with diltiazem 180 mg/day, atenolol 50 mg/day or amlodipine 5 mg/day, the total exercise duration (TED) was significantly better in the RANEXA 750 mg twice daily + ongoing treatment group compared to the placebo + ongoing treatment group: difference of 23.7 seconds [2.3; 45.1], \(p=0.03\). It should be noted that 43% of the study patients were not controlled by a non-optimal dose of atenolol (50 mg/day).

**MERLIN study (CVT 3036)**
Method: randomised, double-blind study comparing RANEXA 1000 mg twice daily combined with standard treatment to placebo in 6,541 patients with acute coronary syndrome without ST segment elevation, monitored over 12 months.

Inclusion criteria: patients aged over 18,
- hospitalised for acute coronary syndrome without ST segment elevation, occurring for over 10 minutes and correlated to myocardial ischaemia,
- with at least one ischemic symptom at rest (\(\geq 5\) minutes) within 48 hours prior to inclusion,
- with a moderate to high risk of cardiovascular event: elevated troponin, ST segment depression (≥ 0.1 mV), diabetes mellitus, TIMI risk score for unstable angina / N STE MI ≥ 3.

**Treatments:**
- RANEXA 1000 mg twice daily, n=3,268
- Placebo, n=3,273

**Primary endpoint:** composite endpoint associating cardiovascular mortality, myocardial infarction and ischaemic event recurrences.

**RESULTS:** on intention-to-treat basis (see table 2)
Baseline patient characteristics were all similar.

**Table 2: number (%) of cardiovascular events observed after 12 months’ treatment**

<table>
<thead>
<tr>
<th></th>
<th>RANEXA 1000 mg twice daily n=3,268</th>
<th>Placebo n=3,273</th>
<th>Relative risk [95%CI] p versus placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events (%)</td>
<td>695 (21.3)</td>
<td>753 (23)</td>
<td>0.92 [0.83; 1.02] NS</td>
</tr>
</tbody>
</table>

After 12 months’ treatment, no statistically significant difference in terms of cardiovascular events (composite endpoint associating cardiovascular mortality, myocardial infarction and ischaemic event recurrences) was observed between the two treatment groups: 695/3,268 (21.3%) patients in the RANEXA 1000 mg twice daily group versus 753/3,273 (23%) patients in the placebo group, RR 0.92 [0.83–1.02], NS.

**3.2. Adverse effects**
Tolerance was evaluated out of a total 9,744 RANEXA patients compared to 5,108 taking the placebo. The adverse events proved to be dose-dependent.

**MARISA Study:**
Adverse events were observed in 10/181 patients (5%) in the RANEXA 500 mg twice daily group and 9/179 (5%) in the placebo group.
The most frequent adverse events were:
- angina: 2/181 patients on RANEXA compared to 1/179 taking the placebo
- dizziness: 2/181 patients on RANEXA compared to 1/179 taking the placebo

**CARISA study:**
Adverse events were observed in 41/279 patients (14.7%) in the RANEXA 750 mg twice daily group compared with 17/269 (6.3%) in the placebo group.
The most frequent adverse events were:
- gastrointestinal disorders (constipation, dyspepsia, nausea): 28/279 (10%) patients on RANEXA compared to 6/269 (2.2%) taking the placebo,
- asthenia: 3/279 compared to 0,
- headaches: 4/279 compared to 1/269,
- dizziness: 6/279 compared to 4/269.

**MERLIN study:**
Adverse events were observed in 992/3,268 patients (30%) in the RANEXA group compared with 675/3,273 (21%) in the placebo group.
The most frequent adverse events were:
- gastrointestinal disorders (constipation, nausea, vomiting, diarrhoea): 459/3,268 (14%) on RANEXA compared to 235/3,273 (7%) taking the placebo,
- dizziness: 7% compared to 3%.  

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3.3. Conclusion

The efficacy and tolerance of RANEXA were evaluated in three comparative studies on patients with stable angina.

In the MARISA study, after 4 weeks of treatment, the total exercise duration (TED) was significantly improved with RANEXA 500 mg twice daily compared to placebo: difference = 23.8 seconds [8.2; 39.4] p = 0.003.

In the CARISA study, after 12 weeks of treatment, in patients inadequately controlled with diltiazem 180 mg/day, atenolol 50 mg/day or amlodipine 5 mg/day, the total exercise duration (TED) was significantly improved in the RANEXA 750 mg twice daily + ongoing treatment group compared to the placebo + ongoing treatment group: difference of 23.7 seconds [2.3; 45.1], p=0.03. It should be noted that 43% of the study patients were not controlled by a non-optimal dose of atenolol (50 mg/day).

In the MERLIN study, after 12 months’ treatment combined with standard treatments, no statistically significant difference in terms of cardiovascular events (composite endpoint associating cardiovascular mortality, myocardial infarction and ischaemic event recurrences) was observed between the treatments: 695/3,268 (21.3%) patients in the RANEXA 1000 mg twice daily group versus 753/3,273 (23%) in the placebo group, RR 0.92 [0.83–1.02], NS.

The most common adverse effects observed in these studies were: gastrointestinal disorders (constipation, dyspepsia, nausea), dizziness, asthenia, headaches and angina.

There is no study currently available comparing the efficacy of RANEXA with nicorandil (ADANCOR, IKOREL) or ivabradine (PROCORALAN).
4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit
Stable chronic angina is generally the clinical sign of ischaemic heart disease. It is a frequent and serious disorder that may be life-threatening.

The efficacy/adverse effects ratio of RANEXA is high.

RANEXA provides symptomatic treatment, aiming to improve symptoms and prevent recurrences of angina attacks.

RANEXA is a second-line treatment for patients whose condition is inadequately controlled with first-line treatments (betablockers and/or calcium channel inhibitors) or who are intolerant to the latter.

There are alternative treatments.

Public health benefit:
Stable chronic angina is a frequent and serious condition. As the population that may benefit from RANEXA treatment is limited to patients inadequately controlled or with a contraindication or intolerance to first-line antianginals (betablockers and/or calcium channel blockers), the public health burden may be considered to be low. Improvement in the management of ischaemic heart disease is a public health need that falls within the scope of identified priorities (Public Health Act 2004, GTNDO*).

Given the results of the studies available (efficacy in terms of morbidity and mortality compared to placebo not demonstrated), this product is not expected to have any impact on morbidity and mortality. RANEXA is therefore not expected to provide a solution to the identified public health need.

Consequently, RANEXA is not expected to have an impact on public health.

The actual benefit of RANEXA in this indication is substantial.

4.2. Improvement in actual benefit
RANEXA should be used only by patients with stable angina that is inadequately controlled or who are intolerant to betablockers and/or calcium channel blockers.

Given the data available, RANEXA does not provide any improvement in actual benefit (IAB V) in the management of these patients.

4.3. Therapeutic use
According to the guidelines of the European Society of Cardiology, in addition to secondary preventive measures (lifestyle and dietary measures, aspirin, statins) indicated in coronary artery disease, symptomatic treatment of stable angina serves to improve symptoms and prevent the recurrence of angina attacks.

First-line treatment involves the use of beta-blockers which reduce myocardial oxygen requirements by a combination of negative inotropic, negative chronotropic rate-limiting effects and a slight reduction in systolic blood pressure, and revascularization by angioplasty and/or aortocoronary bypass surgery in patients who are refractory to medication.

Rate-limiting (verapamil, diltiazem) or non-rate limiting (amlodipine, etc.) calcium channel blockers, long-acting nitrates and nicorandil may be used alone or in combination with

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betablockers (non-rate limiting blockers and nitrates) and in particular for second-line therapy in the event of contraindications or intolerance to betablockers.

Ivabradine may be used as second-line treatment in patients with a normal sinus rhythm, who have a contraindication or are intolerant to betablockers or a contraindication to rate-limiting calcium channel blockers.

RANEXA (ranolazine) can be used by patients with inadequately controlled stable angina or who are intolerant to betablockers and calcium channel blockers.

4.4. Target population
RANEXA's target population is comprised of patients with chronic stable angina poorly controlled despite optimal antianginal management including medication recommended in first-line treatment (betablockers and calcium channel blockers) and not eligible for coronary revascularisation.

The size of this population can be estimated based on the following data:
- a prevalence of stable angina of around 2 to 2.5% of the general population (Datamonitor Base, 2002; Montaye, 2006; ESC, 2006), i.e. approximately 1.3 to 1.5 million people in France,
- around 27% of patients remain symptomatic despite optimal medicinal treatment with or without revascularisation (Courage study), of which around 10% (Crussade registers 2005; Lindenauer 2005; Daly 2005 and expert opinion) are thought to have a contraindication or be intolerant to betablockers and/or calcium channel blockers,
- 5 to 10% of these patients are not thought to be eligible for initial or another revascularisation (Mannheimer 2002).

On this basis, the maximum target population for RANEXA is thought to be 40,000 patients.

4.5. Transparency Committee recommendations
The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services for the indication and at the dosage stated in the MA.

Packaging: suitable for the prescription requirements.

Reimbursement rate: 65%